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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/017,735	02/03/1998	HOWARD M. GREY	018623-00589	8763

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EXAMINER	
SCHWADRON, RONALD B	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/017,735	GREY ET AL.	
	Examiner	Art Unit	
	Ron Schwadron, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 9-62 is/are pending in the application.

4a) Of the above claim(s) 10,18-20,23-25,27,32,33,42,51,52 and 54-62 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 9,11-17,21,22,26,28-30,34-41,43-50 and 53 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Applicant's election with traverse of Group II in the reply filed on 12/14/2000 is acknowledged. The traversal is on the ground(s) that are stated in said paper. This is not found persuasive because of the following reasons. Regarding applicants comments about undue burden, the M.P.E.P. § 803 states that: "For purposes of the initial requirement, a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search". The restriction requirement enunciated in the previous Office Action meets this criterion and therefore establishes that serious burden is placed on the Examiner by the search of additional Groups.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 24,25,32,33,51,52,55,56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/14/2000.

3. Applicant's election with traverse of the species 10mer, A/M, MASDFNLPPV, CTL attached peptide, pathogen derived peptide, chemically synthesized peptide and in vivo method in the reply filed on 12/14/2000 is acknowledged. The traversal is on the ground(s) that are stated in said paper. Regarding applicants comments, the species election delineated in the Office action mailed 3/27/2000 was the subject of numerous hours of conversation between applicant and the Examiner, SPE Chan and former BPS Schwartz. It was determined during said conversations that the species requirement was necessary and appropriate. Said requirement is in accordance with the rules for species election requirements as per the MPEP.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 10,18-20,23,27,34,42,54,57-62 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/14/2000.

5. Claims 9,11-17,21,22,26,28-31,34-41,43-50,53 are under consideration.

6. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because it does not identify the citizenship of Inventor Sidney.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 9,11-17,21,22,26,28-31,34-41,43-50,53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no support in the specification as originally filed for the method which recites an "epitope consisting of about 8-11 amino acids" with the motif recited in claims 9,31,41 The specification discloses a motif for a 9mer peptide (see original claims 1 and 2 and page 3, line 1), wherein specific residues are found at positions 2 and 9. The specification discloses a motif for a 10mer peptide (see original claims 1 and 2 and page 3, line 1), wherein specific residues are found at positions 2 and 10 (see original claim 3). Regarding claims 9,31,41 the specification does not disclose 8-mer or 11-mer peptides with said motif. For example, there is no disclose in the specification of an 8-mer with V/A/T at position 2 from the amino terminus, with the amino acids at

the carboxy terminus as per recited in the claim (eg. the specification discloses amino acids at position 2 or 9/10 in relation to a 9mer or 10mer, not an 8mer of 11mer).

There is no support in the specification as originally filed for the particular subsets of residues recited at the amino acid terminus/carboxy terminus (eg. they are a "range within a range").

There is no support in the specification as originally filed for the recitation of "connected to another molecule" in claim 9 and 31.

There is also disclosure in the specification as originally filed of the limitation "with a proviso that neither said peptide, said other molecule nor said compound comprise an entire native antigen" in claim 9 or "with a proviso that neither the obtained peptide, the other molecule nor the compound comprise an entire native antigen" in claim 31 or "with a proviso that said peptide, does not comprise an entire native antigen" in claim 41. There is also disclosure in the specification as originally filed of the limitation "with the proviso that the peptide is not an entire native antigen" in claim 26 or similar language in claim 34.

There is no support in the specification as originally filed for the recitation of "pathogenic agent" in claims 11,43.

There is no support in the specification as originally filed for the limitation of claim 14 (or similar language in claim 31 or 47) Regarding applicants comments, the experiment disclosed in pages 37-40 is an in vitro binding method which uses the reference peptide FLPSDYFPSV. This not a disclosure of the scope of the claimed inventions which encompass CTL inducing methods in vivo with a unspecified reference peptide. Regarding the specification, page 76, said passage refers to experiments in transgenic mice, wherein peptide were previously tested in an in vitro method using reference peptide FLPSDYFPSV. This not a disclosure of the scope of the claimed inventions which encompass CTL inducing methods in vivo with a unspecified reference peptide.

There is no support in the specification as originally filed for the claimed invention (it constitutes new matter).

9. The amendment filed 10/9/2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that

no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is SEQ. IDS. 192-195. Said SEQ. IDS. constitute new matter for the same reasons that the motif recited in the claims constitutes new matter as per paragraph 8 of this Office action.

Applicant is required to cancel the new matter in the reply to this Office Action.

10. Claims 9,11-17,21,22,26,28-31,34-41,43-50,53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed inventions.

The instant claims encompass a method that uses immunogenic peptides wherein 2 amino acids at anchor positions are specified. The other amino acids of the peptide are not specified. The claims recite that the peptide elicits a CTL response. The specification discloses that the two amino acids recited in the claim are pertinent to HLA binding of said peptides. However, the art recognizes that in order to generate a CTL response, a peptide must bind MHC and also present *an epitope recognized by T cells*. The art recognizes that the T cell epitope differs from the amino acids pertinent to MHC binding. There is no written description in the specification of the amino acids that constitute the T cell epitope in the peptide recited in the claim. Therefore, the skilled artisan cannot envision the detailed structure of the encompassed peptides used in the claimed method and therefore conception is not achieved until reduction to practice has

occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. In the instant application, the amino acid itself or isolated peptide is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016. In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein. See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1404-7 (Fed. Cir. 1997). In University of California v. Eli Lilly and Co., 39 U.S.P.Q.2d 1225 (Fed. Cir. 1995) the inventors claimed a genus of DNA species encoding insulin in different vertebrates or mammals, but had only described a single species of cDNA which encoded rat insulin. The court held that only the nucleic acids species described in the specification (i.e. nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, id. at 1240. The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials. . .conception has not been achieved until reduction to practice has occurred", Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd., 18 U.S.P.Q.2d 016 (Fed. Cir. 1991). Attention is also directed to the decision of The Regents of the University of California v. Eli Lilly and Company (CAFC, July 1997) wherein is stated: "The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the

recitation of the sequence of nucleotides that make up the cDNA." See Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606.

10. Claims 9,11-17,21,22,26,28-31,34-41,43-50,53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention.

The specification is not enabling for the claimed methods of inducing a CTL response. The claimed methods encompass in vivo administration of the recited peptides to humans wherein the utility for said method is in vivo treatment of disease. It is unpredictable based on the disclosure of the specification as to whether the claimed methods could be used to treat disease in vivo in humans. The specification provides no evidence that the peptides recited in the claims elicit a CTL response in humans and wherein the administered peptides would be used to treat disease in vivo in humans. The only specific and substantive utility for the claimed method disclosed in the specification is in vivo treatment of disease in humans. It would require undue experimentation to determine which of the trillions of peptides encompassed by the motif recited in the claims elicit a CTL response in vivo and could be used to treat disease and which do not. Celis et al. teach that in order to establish whether a peptide is immunogenic said peptide needs to be tested in assays that actually establish that a peptide is immunogenic (eg. CTL assay, etc.). Celis et al. teach that:

"In addition to MHC binding, other factors such as antigen processing, peptide transport and the composition of the T-cell receptor repertoire could determine whether any of these peptides can function as effective CTL antigens". Further, although *experimental* ranking schemes are available for predicting relative binding strengths of some HLA binding nonapeptides, and assays are available to test the binding of peptides to HLA, an undue amount of experimentation would be involved in determining peptides from the many possibilities that would be capable of binding to HLA and inducing a CTL response. Ochoa-Garay et al (Molecular Immunol.) teach that "In summary, the results in this report indicate that the immunogenicity of a peptide cannot always be predicted from its affinity for class I or the presence of class I binding motifs.

In addition, our data show that variables such as CTL precursor frequency, peptide hydrophobicity and stability can influence the in vitro induction of CTL responses" (especially page 279, last sentence and continuing onto page 280). Karin et al (J. Exp. Med. 180: 2227-2237, 1994) teach that amino acids in an MHC binding peptide that are not the amino acids which participate in MHC binding can have a profound effect on whether or not a peptide is immunogenic. The claimed invention recites a motif wherein residues not involved in MHC binding are not specified. Karin et al teach that a single substitution in an amino acid, wherein said amino acid plays no role in MHC binding can completely abrogate the immunogenicity of an otherwise immunogenic peptide (especially Summary and Table 1). Thus Karin et al establish that amino acid residues not recited in the claimed peptide (e.e., amino acid residues not involved in MHC binding of a peptide) will play a pivotal role in determining whether the peptides recited in the claims are immunogenic. Rammensee et al. teach that "MHC/peptide binding assays have a history of leading to obsolete result" (see page 182, first column). Rammensee et al. teach problems with interpreting data derived from said assays (see page 182, first column). DiBrino et al (J. Immunology) teach that the presence of anchor residues is not sufficient for binding to HLA because peptides with optimal amino acid residues at anchor positions failed to bind. Van der Most et al (J. Immunol. and Virology) teach that although an antigenic protein may contain multiple motif-fitting peptides, CTL responses are usually directed against a very limited number of immunodominant epitopes and that immunodominance appears to be determined by a variety of factors including binding affinity to HLA (and motif binding peptides bind with a wide range of affinities due to secondary anchor residues and secondary effects), intracellular processing of peptides determines whether at which level a particular peptide will be presented at the cell surface, and holes in the T cell repertoire restrict CTL responses. Van der Most et al also teach that a peptide from NP with the second highest binding affinity (IC50= 4.8nM) after the immunodominant peptide for L^d, is not recognized by LCMV-restricted CTLs. Chang et al (J. Immunol.) teach a peptide that was immunogenic in only a single patient despite similar HLA-binding affinity. Vitiello et al (J. Immunol.) teach the importance of not only binding affinity, but also of availability of specific TCRs and antigen processing in the shaping of the final repertoire of CTL specificities. Bergman et

al (J Virol.) teach a discrepancy between antigenicity and immunogenicity, i.e., failure to induce CTL despite highly efficient recognition in vitro. The length of the peptide is important for binding to HLA (along with the presence of anchor (or motif) amino acid residues present within the peptide). The peptides that bind to class I molecules have a predominant length. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets located at opposite ends of the binding groove of the class I molecule, giving rise to a common orientation of the peptides in the binding site (Engelhard at page 14, column 1, lines 16-27.) Thus, the amino acid residues at the peptides termini make a network of hydrogen bonds with conserved residues on the sides and bottom of the peptide binding groove of class I molecules. These interactions are important for holding the peptides in the binding groove and for stabilizing the complex (Guo, et al at page 366, column 1 lines 1-10,) "...the preferred length (of the peptide) is determined by the minimum amount of peptide required to span the center of the binding site and optimize the interactions at the ends." (Engelhard at page 14, column 1, lines 23-27). The minimum amount of peptide required to span the binding groove and make favorable contacts with their N- and C-termini may be dependent upon the sequence of the peptide itself since different amino acid residues have different physicochemical properties, and may be dependent upon the identity of the additional amino acids, since these residues may make a negative contribution to binding. Accordingly, there is a high level of unpredictability in designing/selecting longer sequences that would still maintain binding function, and applicant does not provide direction or guidance to do so. Shastri et al (J. Immunology) teach that presentation of endogenous peptide/MHC class I complexes is profoundly influenced by specific C-terminal flanking residues. It would require undue experimentation to determine which of the trillions of peptides encompassed by the peptides recited in the motif recited in the claims did or did not elicit HLA A2.1 restricted CTL and could be used in vivo to treat disease in humans. Further, synthetic peptides that are chosen on the basis of scanning the protein of interest for potential peptide sequences that have a supermotif for binding to an HLA molecule or molecules may not induce a CTL response due to lack of Th support for CTLp to

CTL. There is insufficient guidance in the specification as to how to make the instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 14,31,34-40,47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14,31,34-40,47 are indefinite in the recitation of "standard peptide" because said term has no art recognized meaning in the context recited in the claims and it is not defined in the specification. While the specification discloses one example of a specific peptide used as a standard in the context recited in the claims, it does not define what constitutes a "standard peptide" in terms of binding affinity or any other property.

13. Regarding the application of prior art, for the same reasons that the claimed inventions constitute new matter, the claims are not entitled to priority to the various parent applications to which priority is claimed.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 9,11-17,21,22,26,28-31,34-41,43-50,53 are rejected under 35 U.S.C. 102(b) as being anticipated by Grey et al. (WO 94/20127).

Grey et al. disclose that HLA A2.1 restricted CTL can induced in vivo in humans by administering 10mer peptides derived from a virus (eg. a natural source) that bind HLA 2.1 (see page 3, first paragraph and second paragraph, page 22). The administered peptides form a complex with HLA 2.1 in vivo (a CTL response is only induced by binding of TCR to a CTL/MHC complex). The peptide can have A at the first conserved residue and M at the carboxy terminus (see Grey et al., claim 11). The administered peptide can be a heteropolymer or homopolymer that would have multiple CTL epitopes connected (see page 26). The peptides can be chemically synthesized (see page 20, last paragraph). The 10mer peptide is not a entire native antigen. Grey et al. teach administration of a booster dose of said peptide (se page 22, lines 16-28). Grey et al. teach that the immunogenic peptide should induce a CTL response (see page 3, last paragraph, continued on page 4). Therefore, the peptides used in said method would inherently have the binding affinity recited in the claims because according to Grey et al., such an affinity is required in order to induce CTL (see TABLE 24).

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ron Schwadron, Ph.D. whose telephone number is 571 272-0851. The examiner can normally be reached on Monday to Thursday from 7:30am to 6:00pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at 571 272 0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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